Convenient One-Pot Synthesis of Symmetrical Xanthenes

Lajos Novák,[a] Péter Kovács,[b] György Pirok,[a] Pál Kolonits,[a] Éva Szabó,[c] Jenő Fekete,[c] Viktor Weiszfeiler,[a] Csaba Szántay*[ab]

[a] Institute for Organic Chemistry, Technical University, H-1521 Budapest, Gellért tér 4, Hungary
Fax + 36(1)4633297; E-mail:SZANTAY@CH.BME.HU
[b] Central Research Institute for Chemistry, H-1525 Budapest, P.O.B. 17, Hungary
[c] Institute for General and Analytical Chemistry, Technical University, H-1111 Budapest, Gellért tér 4, Hungary

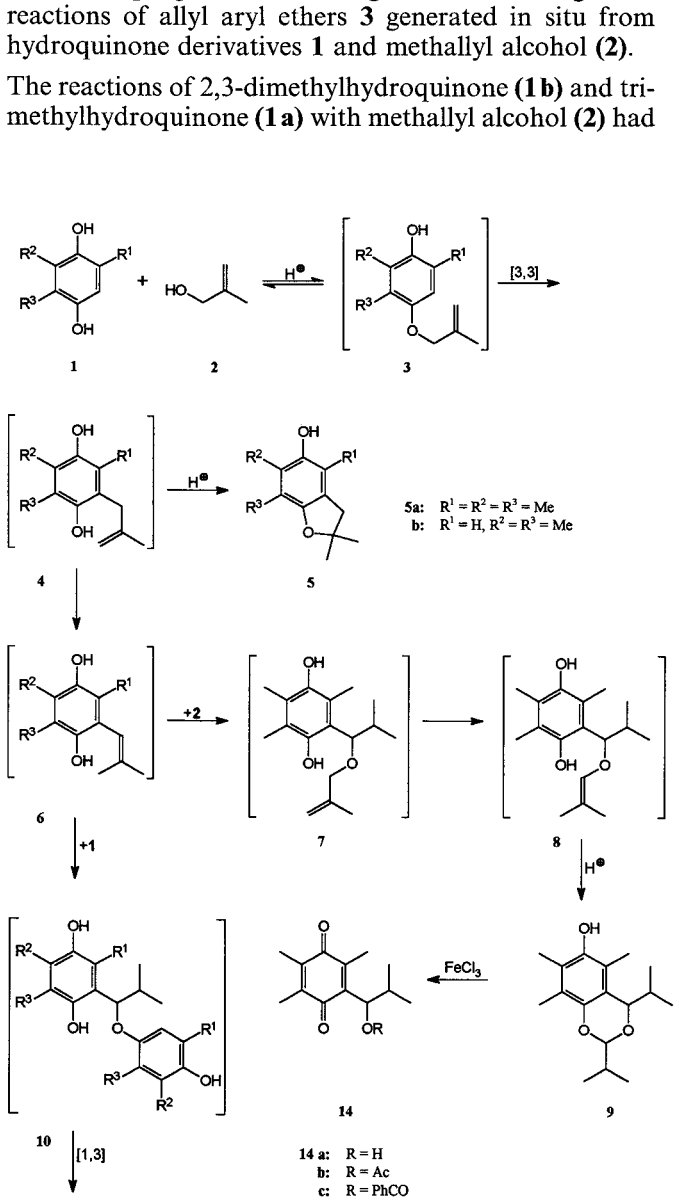
Received 6 December 1994; revised 26 January 1995

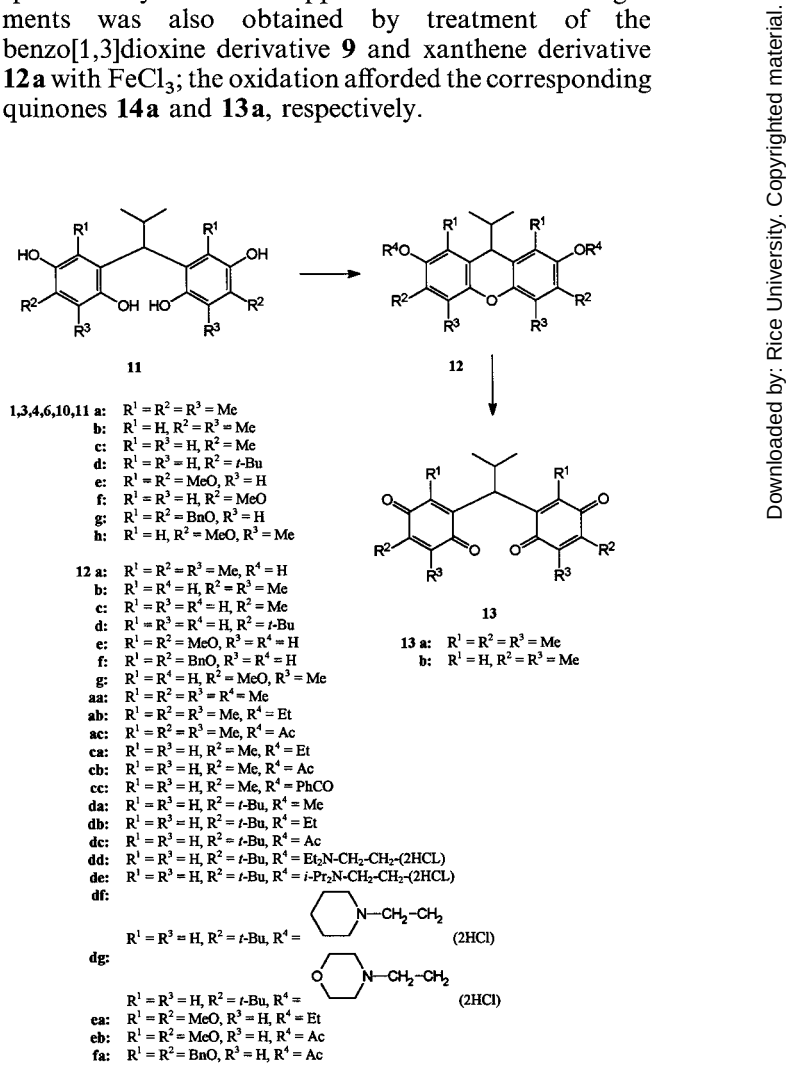
A new method is described for the preparation of symmetrically substituted xanthenes **12**. They were obtained by consecutive rearrangements and intramolecular cyclizations of allyl aryl ethers **3** formed in situ from hydroquinone derivatives **1** and methallyl alcohol **(2)**.

Sigmatropic rearrangement of allyl aryl ethers provides an efficient and selective method for constructing carbon–carbon bonds and has been increasingly employed in synthesis.[1–4] Recently, we reported the reactions of hydroquinone derivatives with but-2-ene-1,4-diol providing a new synthesis of vinylbenzofurans.[5] Continuing our program, we investigated the rearrangement reactions of allyl aryl ethers **3** generated in situ from hydroquinone derivatives **1** and methallyl alcohol **(2)**.

The reactions of 2,3-dimethylhydroquinone **(1b)** and trimethylhydroquinone **(1a)** with methallyl alcohol **(2)** had been investigated by Lars et al.[6] and Ingold et al.[7] They performed the reactions in anhydrous formic acid in the presence of catalytic amounts of H_2SO_4 and isolated the benzofurans **5b** and **5a** in poor yields (29 and 12%, respectively).

When the above reaction (**1a** and **2**) was performed in dry toluene at 80 °C using TsOH as catalyst, besides the same benzofuran **5a** the formation of two other compounds, **9** and **12a**, was also observed (Scheme 1). The structures of these new compounds, isolated by column chromatography, were established by NMR and mass spectrometry. Chemical support for the structural assignments was also obtained by treatment of the benzo[1,3]dioxine derivative **9** and xanthene derivative **12a** with $FeCl_3$; the oxidation afforded the corresponding quinones **14a** and **13a**, respectively.





Scheme 1

Downloaded by: Rice University. Copyrighted material.

Table 1. Xanthenes **12a–g** Prepared

Product	Starting Material	Solvent	Reaction		Yield (%)	Mp (°C)	TLC[a] (R_f)	HPLC R_t (min)
			Temp. (°C)	Time (h)				
12a	**1a**	CH_2Cl_2	40	14	85	199–200	0.34	8.8[b]
12b	**1b**	toluene	70	30	16	165	0.4	
12c	**1c**	toluene	70	30	44	188–190	0.34	5.8[c]
12d	**1d**	toluene	70	24	57	235–237	0.47	15[d]
12e	**1e**	toluene	70	5	58	193–194	0.5	2.8[c]
12f	**1g**	toluene	70	10	58	126–127	0.4	17.5[d]
12g	**1h**	toluene	70	20	52	191–194	0.46	21.3[b]

[a] Hexane/acetone (5 : 2).
[b] Hexane/CH_2Cl_2/*i*-PrOH (50 : 50 : 0.5).
[c] Acetonitrile/H_2O (60 : 40).
[d] Hexane/CH_2Cl_2/dioxane (80 : 20 : 0.25).

Table 2. Spectral Data for Substituted 2,7-Dihydroxy-9*H*-xanthenes

Product	IR ν_{max} (cm^{-1})	^1H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) δ, J (Hz)	MS *m/z* (%)
12a	3410, 1460, 1410, 1380, 1210, 1080	4.06 (1H, d, J = 6, CH), 4.34 (2H, s, 2OH) 12.17 (6ArMe), 20.24, (C-2′ and C-3′), 36.01 (C-1′), 41.01 (C-9), 118.06 (C-1 and C-8), 120.63 (C-4 and C-5), 22.18 (C-3 and C-7), 124.26 (C-4b and C-8a), 146.96 (C-2 and C-7), 147.43 (C-4a and C-8b)	340 (M^+, 8), 298 (17), 297 ($M^+ - C_3H_7$, 100)
12b	3400, 3200, 1460, 1410, 1380, 1350, 1205, 1075	0.74 (6H, d, J = 6, $2CH_3$), 1.75 (1H, m, CH), 2.07 (6H, s, $2CH_3$), 2.23 (6H, s, $2CH_3$), 3.50 (3H, m, 2OH, CH), 6.50 (2H, s, H_{arom}) 11.79 (C-4-CH_3 and C-5-CH_3), 11.97 (C-3-CH_3 and C-6-CH_3), 19.25 (C-2′ and C-3′), 36.60 (C-1′), 46.19 (C-9), 112.07 (C-1 and C-8), 121.60 (C-4 and C-5), 121.72 (C-3 and C-6), 123.80 (C-4b and C-8a), 144.60 (C-2 and C-7), 149.83 (C-4a and C-8b)	312 (M^+, 4), 270 (21), 269 ($M^+ - C_3H_7$, 100), 128 (18)
12c	3300, 1460, 1410, 1380, 1190, 1180, 1060	0.78 (6H, d, J = 6, $2CH_3$), 1.87 (1H, m, CH), 2.19 (6H, s, $2CH_3$), 3.56 (1H, d, J = 4, CH), 6.59 (2H, s, H_{arom}), 6.75 (2H, s, H_{arom}), 8.35 (2H, s, 2OH) 15.77 (C-3-CH_3 and C-6-CH_3), 18.96 (C-2′ and C-3′), 37.13 (C-1′), 44.99 (C-9), 114.76 (C-1 and C-8), 117.25 (C-4 and C-5), 121.60 (C-3 and C-6), 123.42 (C-4b and C-8a), 145.77 (C-2 and C-7), 150.45 (C-4a and C-8b)	284 (M^+, 10), 241 ($M^+ - C_3H_7$, 100), 211 (10), 198 (4)
12d	3520, 1520, 1430, 1380, 1310, 1210	0.78 (6H, d, J = 6.5, $2CH_3$), 1.40 (18H, s, 2*t*-Bu), 1.88 (1H, m, CH), 3.52 (1H, d, J = 4, CH), 6.53 (2H, s, H_{arom}), 6.93 (2H, s, H_{arom}), 7.59 (2H, s, 2OH)	368 (M^+, 5), 325 ($M^+ - C_3H_7$, 100), 310 (14), 295 (15)
12e	3430, 1470, 1450, 1430, 1390, 1350, 1310, 1270, 1240, 1220, 1190, 1110, 1100, 1090	0.78 (6H, d, J = 7, $2CH_3$), 1.89 (1H, m, CH), 3.87 (6H, s, $2OCH_3$), 3.92 (6H, s, $2OCH_3$), 4.28 (1H, d, J = 5, CH), 5.28 (2H, br s, 2OH), 6.46 (2H, s, H_{arom}) 19.51 (C-2′ and C-3′), 35.10 (C-9), 56.43 (C-3-OCH_3 and C-6-OCH_3), 60.67 (C-1-OCH_3 and C-8-OCH_3), 95.45 (C-4 and C-5), 111.92 (C-4b and C-8a), 134.44 (C-2 and C-7), 144.56 (C-1 and C-8), 146.37 (C-3 and C-6), 147.25 (C-4a and C-8b)	376 ($M^+ < 1$), 333 ($M^+ - C_3H_7$, 100), 318 (6), 299 (5)
12f	3600, 3500, 1500, 1460, 1390, 1300, 1260, 1240, 1210, 1190, 1100, 1080	0.76 (6H, d, J = 7, $2CH_3$), 1.95 (1H, m, CH), 4.43 (1H, d, J = 4, CH), 4.96 and 5.10 (4H, ABq, J = 12, gem. hydrogens of C-1 and C-8-benzyloxy CH_2), 5.09 and 5.11 (4H, ABq, J = 11, gem. hydrogens of C-1- and C-8-benzyloxy CH_2), 5.85 (2H, s, 2OH), 6.55 (2H, s, C-4-H and C-5-H), 7.27 (8H, m, H_{arom}), 7.42 (12H, m, H_{arom})	680 (M^+, < 1), 637 ($M^+ - C_3H_7$, 15), 547 (10), 455 (8), 91 (100)
12g	3400, 1500, 1460, 1390, 1360, 1260, 1210, 1130, 1100, 1080	0.79 (6H, d, J = 7, $2CH_3$), 1.86 (1H, m, CH), 2.34 (6H, s, $2CH_3$), 3.55 (1H, d, J = 4.5, CH), 3.80 (6H, s, $2OCH_3$), 5.39 (2H, s, 2OH), 6.61 (2H, s, H_{arom}) 9.50 (C-4-CH_3 and C-5-CH_3), 19.29 (C-2′ and C-3′), 37.04 (C-1′), 46.60 (C-9), 61.07 ($2OCH_3$), 111.97 (C-1 and C-8), 118.40 (C-4 and C-5), 120.62 (C-4b and C-8a), 143.83 (C-2 and C-7), 144.10 (C-3 and C-6), 145.34 (C-4a and C-8b)	344 (M^+, 7), 301 ($M^+ - C_3H_7$, 100), 286 (12), 271 (26)
12aa	1470, 1400, 1380, 1350, 1280, 1230, 1090, 1000	0.78 (6H, d, J = 7, $2CH_3$), 1.80 (1H, m, CH), 2.23 (6H, s, $2CH_3$), 2.31 (6H, s, $2CH_3$), 2.33 (6H, s, $2CH_3$), 3.64 (6H, s, $2CH_3O$), 3.99 (1H, d, J = 4, CH)	368 (M^+, < 1), 325 ($M^+ - C_3H_7$, 100), 311 (10), 282 (5)
12ab	1480, 1470, 1420, 1400, 1380, 1280, 1240, 1100	0.78 (6H, d, J = 6, $2CH_3$), 1.42 (6H, t, J = 7, $2CH_3$), 1.80 (1H, m, CH), 2.22 (6H, s, $2CH_3$), 2.30 (6H, s, $2CH_3$), 2.34 (6H, s, $2CH_3$), 3.72 (4H, q, J = 7, $2CH_2O$), 3.98 (1H, d, J = 5, CH)	396 (M^+, 1), 353 ($M^+ - C_3H_7$, 100), 325 (5), 296 (5), 267 (6)
12ac	1750, 1470, 1410, 1370, 1320, 1190, 1060, 1020	0.78 (6H, d, J = 6, $2CH_3$), 1.80 (1H, m, CH), 2.14 (6H, s, $2CH_3$), 2.25 (6H, s, $2CH_3$), 2.66 (12H, s, $2CH_3$ and 2Ac), 3.98 (1H, d, J = 4, CH)	424 (M^+, < 1), 381 ($M^+ - C_3H_7$, 100), 339 (20), 297 (25)
12ca	1580, 1500, 1480, 1450, 1410, 1380, 1330, 1290, 1250, 1200	0.79 (6H, d, J = 7, $2CH_3$), 1.41 (6H, t, J = 6, $2CH_3$), 1.9 (1H, m, CH), 2.21 (6H, s, $2CH_3$), 3.67 (1H, d, J = 4, CH), 4.00 (4H, m, 2q, J = 7, $2CH_2O$), 6.58 (2H, s, H_{arom}), 6.85 (2H, s, H_{arom})	

Downloaded by: Rice University. Copyrighted material.

Table 2. (continued)

Product	IR ν_{max} (cm^{-1})	^1H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) δ, J (Hz)	MS m/z (%)
12cb	1760, 1580, 1500, 1450, 1410, 1380, 1360, 1300, 1250, 1210, 1190, 1160	0.78 (6H, d, J = 7, $2CH_3$), 1.89 (1H, m, CH), 2.15 (6H, s, $2CH_3$), 2.3 (6H, s, 2Ac), 3.68 (1H, d, J = 4, CH), 6.8 (2H, s, H_{arom}), 6.93 (2H, s, H_{arom})	368 (M^+, 2), 325 ($M^+ - C_3H_7$, 100), 283 (42), 241 (50)
12cc	1750, 1740, 1480, 1440, 1410, 1390, 1250, 1150, 1080, 1030	0.83 (6H, d, J = 7, $2CH_3$), 1.97 (1H, m, J = 7 and 4, CH), 2.23 (6H, s, $2CH_3$), 3.75 (1H, d, J = 4, CH), 6.96 (2H, s, H_{arom}), 7.00 (2H, s, H_{arom}), 7.52 (4H, mt, J = 8, H_{arom}), 7.65 (2H, mt, J = 8, H_{arom}), 8.23 (4H, m, J = 8 and 1.5, H_{arom})	
12da	1580, 1500, 1460, 1380, 1360, 1310, 1280, 1270, 1200, 1170	0.82 (6H, d, J = 7, $2CH_3$), 1.37 (18H, s, 2*t*-Bu), 1.97 (1H, m, J = 7 and 4, CH), 3.70 (1H, d, J = 4, CH), 3.82 (6H, s, $2CH_3O$), 6.62 (2H, s, H_{arom}), 7.00 (2H, s, H_{arom})	396 (M^+, 2), 353 ($M^+ - C_3H_7$, 100), 323 (6), 393 (3)
12db	1580, 1500, 1480, 1380, 1330, 1300, 1210, 1180	0.82 (6H, d, J = 7, $2CH_3$), 1.38 (18H, s, 2*t*-Bu), 1.45 (6H, t, J = 7, $2CH_3$), 1.95 (1H, m, J = 7 and 4, CH), 3.66 (1H, d, J = 4, CH), 4.01 (4H, m, $2CH_2O$), 6.60 (2H, s, H_{arom}), 6.99 (2H, s, H_{arom})	424 (M^+, 3), 381 ($M^+ - C_3H_7$, 100), 365 (3), 337 (6)
12dc	1750, 1480, 1360, 1290, 1200, 1170	0.71 (6H, d, J = 7, $2CH_3$), 1.35 (18H, s, 2*t*-Bu), 1.92 (1H, m, CH), 2.32 (6H, s, 2Ac), 3.67 (1H, d, J = 4, CH), 6.80 (2H, s, H_{arom}), 7.08 (2H, s, H_{arom})	452 (M^+, < 1), 409 ($M^+ - C_3H_7$, 100), 367 (20), 351 (5), 325 (14)
12dd	2420, 1580, 1500, 1470, 1420, 1400, 1380, 1290, 1245, 1200	0.82 (6H, d, J = 6.5, $2CH_3$), 1.36 (18H, s, 2*t*-Bu), 1.50 (12H, t, J = 7, $4CH_3$), 1.97 (1H, m, CH), 3.30 (10H, m, $4CH_2N$, 2NH), 3.51 (4H, m, $2CH_2N$), 3.73 (1H, d, J = 4, CH), 4.58 (4H, m, $2CH_2O$), 6.73 (2H, s, H_{arom}), 7.00 (2H, s, H_{arom})	566 (M^+, 2), 523 ($M^+ - C_3H_7$, 53), 424 (2), 100 (100), 86 (68)
12de	3500, 2700, 2420, 1580, 1500, 1470, 1420, 1400, 1370, 1320, 1290, 1240, 1200, 1170, 1060	0.81 (6H, d, J = 7, $2CH_3$), 1.35 (18H, s, 2*t*-Bu), 1.56 (24H, d, J = 6.5, $8CH_3$), 1.99 (1H, m, CH), 3.43 (4H, t, J = 7, $2CH_2N$), 3.76 (1H, d, J = 6.5, CH), 3.81 (4H, sept, J = 6.5, 4CH), 4.66 (4H, m, $2OCH_2$), 6.78 (2H, s, H_{arom}), 7.00 (2H, s, H_{arom}), 11.68 (2H, br s, $2NH^+$) 17.99 ($NCHCH_3$), 18.46 ($NCHCH_3$), 19.25 (C-2′ and C-3′), 30.19 (CCH_3), 34.74 (C-3-C and C-6-C), 37.35 (C-1′), 45.60 (C-9), 45.98 (CH_2N), 54.82 (NCH), 64.62 (OCH_2), 114.34 (C-4 and C-5), 114.75 (C-1 or C-8), 114.87 (C-8 or C-1), 122.21 (C-4b or C-8a), 122.27 (C-8a or C-4b), 138.18 (C-3 or C-6), 138.27 (C-6 or C-3), 147.92 (C-2 and C-7), 152.08 (C-4a and C-8b)	622 (M^+, 3), 579 ($M^+ - C_3H_7$, 18), 452 (1), 128 (83), 114 (100)
12df	1580, 1500, 1460, 1410, 1380, 1200, 1190, 1170, 1080, 1010	0.81 (6H, d, J = 7, $2CH_3$), 1.36 (18H, s, 2*t*-Bu), 1.97 (1H, m, J = 7 and 4, CH), 2.0 (12H, m, $6CH_2$), 2.95 (4H, m, $2CH_2N$), 3.46 (4H, t, J = 5, $2CH_2N$), 3.64 (4H, m, $2CH_2N$), 3.72 (1H, d, J = 4, CH), 4.58 (4H, m, $2CH_2O$), 6.72 (2H, s, H_{arom}), 7.00 (2H, s, H_{arom}), 11.60 (2H, br s, $2NH^+$)	590 (M^+, 2), 547 ($M^+ - C_3H_7$, 41), 436 (2), 112 (100), 98 (46)
12dg	1580, 1500, 1450, 1400, 1370, 1220, 1190, 1080	0.81 (6H, d, J = 7, $2CH_3$), 1.37 (18H, s, 2*t*-Bu), 1.98 (1H, m, CH), 3.12 (4H, m, $2CH_2N$), 3.52 (4H, m, $2CH_2N$), 3.64 (4H, m, $2CH_2O$), 3.72 (1H, s, CH), 4.04 (4H, m, $2CH_2O$), 4.30 (4H, m, $2CH_2O$), 4.61 (4H, m, $2CH_2O$), 6.73 (2H, s, H_{arom}), 7.00 (2H, s, H_{arom}), 13.50 (2H, br s, $2NH^+$)	594 (M^+, 2), 551 ($M^+ - C_3H_7$, 72), 438 (2), 114 (100), 100 (32)
12ea	1580, 1500, 1380, 1360, 1210, 1080	0.78 (6H, d, J = 7, $2CH_3$), 1.38 (6H, t, J = 6, $2CH_3$), 1.84 (1H, m, CH), 3.83 (6H, s, $2OCH_3$), 3.94 (6H, s, $2OCH_3$), 4.04 (4H, m, $2CH_2O$), 4.26 (1H, d, J = 4, CH), 6.45 (2H, s, H_{arom})	432 (M^+, 1), 389 ($M^+ - C_3H_7$, 100), 359 (7), 345 (5)
12eb	1740, 1580, 1380, 1220, 1180, 1080	0.76 (6H, d, J = 7, $2CH_3$), 1.82 (1H, m, CH), 2.35 (6H, s, $2COCH_3$), 3.82 (6H, s, $2OCH_3$), 3.83 (6H, s, $2OCH_3$), 4.21 (2H, d, J = 4, CH), 6.51 (2H, s, H_{arom})	
12fa	1760, 1630, 1610, 1580, 1500, 1480, 1460, 1380, 1370, 1250, 1170, 1060	0.76 (6H, d, J = 7, $2CH_3$), 1.90 (1H, m, CH), 2.14 (6H, s, $2COCH_3$), 4.34 (1H, d, J = 4, CH), 4.90 (4H, d, J = 12, $2CH_2$), 5.06 (4H, d, J = 5, $2CH_2$), 6.58 (2H, s, H_{arom}), 7.2–7.45 (2OH, m, H_{arom})	764 (M^+ < 1), 721 ($M^+ - C_3H_7$, 54), 679 (3), 91 (100)

Surprisingly, while performing the reaction (**1a** and **2**) in CH_2Cl_2 at lower temperature (40 °C) we observed the exclusive formation of xanthene **12a** isolated in excellent yield (85%). The generality and scope of the above reaction were demonstrated with the reactions of a variety of hydroquinones **1c–e,g,h** with **2** providing xanthenes **12c–g** in good yields (Table 1).

In contrast, the reaction of **1b** with **2** under similar conditions yielded xanthene **12b** in only 16% yield, together with the hydroquinone **11b** being probably an intermediate in the reaction. Furthermore, hydroquinone **11f** was the sole product arising from the reaction of **1f** and **2**. Here, this intermediate had poor solubility in toluene and precipitated from the solution.

Scheme 1 shows a reasonable pathway we propose for the formation of xanthene **12**. The acid-catalyzed reaction between **1** and **2** gives rise to ether **3**, which then undergoes [3,3]-rearrangement to produce intermediate **4**. Double-bond migration in the latter, followed by acid-catalyzed addition of **1** on the so-formed intermediate **6** affords **10**. A [1,3]-migration of the side chain of **10** furnishes intermediate **11** which then undergoes cyclization to yield xanthene **12**.

Likewise, the formation of **9** can be considered to proceed via intermediate **6a**. Namely, acid-catalyzed addition of **2**, followed by double-bond migration in the product **7** affords **8**, which then undergoes intramolecular cyclization to give compound **9**.

Downloaded by: Rice University. Copyrighted material.

Table 3. Xanthene Derivatives **12aa–12fa** Prepared

Product	Starting Material	Reagent	Yield (%)	mp (°C)	TLC R_f	HPLC R_t (min)
12aa	**12a**	$(MeO)_2SO_2$	73.8	117–118	0.56[a]	6.12[h]
12ab	**12a**	$(EtO)_2SO_2$	56	145–146	0.7[a]	7.30[h]
12ac	**12a**	Ac_2O	80.5	176–177	0.26[a]	13.23[i]
12ca	**12c**	$(EtO)_2SO_2$	52	90–91	0.8[b]	10.75[e]
12cb	**12c**	Ac_2O	72.7	146–148	0.45[c]	18.93[f]
12cc	**12c**	C_6H_5COCl	67.8	144	0.6[e]	
12da	**12d**	$(MeO)_2SO_2$	71	149–153	0.85[a]	4.53[g]
12db	**12d**	$(EtO)_2SO_2$	64	98	0.75[b]	7.60[g]
12dc	**12d**	Ac_2O	83	168–170	0.42[a]	13.8[e]
12dd	**12d**	$Et_2NCH_2CH_2Cl$	69	226–232		3.65[g]
12de	**12d**	$i\text{-}Pr_2NCH_2CH_2Cl$	62	155–161		3.85[g]
12df	**12d**	2-(1-piperidyl)ethyl chloride	53	220–226		
12dg	**12d**	2-morpholinoethyl chloride	69	220		2.66[g]
12ea	**12e**	$(EtO)_2SO_4$	54	99–101	0.8[a]	16.5[f]
12eb	**12e**	Ac_2O	52	163–164	0.43[d]	
12fa	**12f**	Ac_2O	73	115–117	0.65[a]	

[a] Hexane/toluene/acetone (60 : 20 : 5).
[b] Hexane/acetone (10 : 1).
[c] Hexane/acetone (5 : 2).
[d] Hexane/toluene/acetone (10 : 5 : 2).
[e] Hexane/CH_2Cl_2/dioxane (80 : 20 : 0.5).
[f] Hexane/CH_2Cl_2/dioxane (90 : 1 : 0.25).
[g] Acetonitrile/H_2O/H_3PO_4 (90 : 10 : 0.25).
[h] Acetonitrile/H_2O/H_3PO_4 (80 : 20 : 0.25).
[i] Acetonitrile/H_2O/H_3PO_4 (60 : 40 : 0.5).

An alternative mechanism for the formation of intermediate **11** would involve direct aromatic electrophilic substitution between **1** and **2** followed by double-bond migration and electrophilic substitution reaction between the formed **6** and **1**.

A wide range of new xanthene derivatives **12aa–fa** were prepared via standard alkylation and acylation process using **12a–g** and the required alkylation and acylation reagents (Table 3).

In conclusion, we have developed a facile, practical route for the preparation of symmetrically substituted xanthene derivatives. Our method has the advantage of simple reaction conditions, convenience and good yield. All new compounds are of potential biological interest.

Reagents were obtained from commercial suppliers and were used without further purification. Compounds **1e,f,g** and **h** were prepared by the literature procedures.[8–11] All reactions were conducted under an atmosphere of dry N_2. Melting points were determined on a Büchi apparatus and are uncorrected. IR spectra were obtained with a Spectromom 2000 Spectrophotometer. ^1H and ^{13}C NMR spectra measurements were carried out using a VXR 400 spectrometer. All signals are expressed as δ values downfield from TMS used as an internal standard. MS spectra were obtained on a KRATOS MS25RFA spectrometer. HPLC analyses were performed on a DuPont 830 instrument equipped with UV detector, stationary phase: Partisil 5 (250 × 4.6 mm). Satisfactory microanalyses were obtained for all new compounds: C ± 0.3, H ± 0.3.

Reaction of 2-Methylprop-2-en-1-ol (2) with Trimethylhydroquinone (1a):

To a stirred suspension of **1a** (20.0 g, 0.13 mol) and TsOH (2.0 g) in dry toluene (150 mL) was added dropwise alcohol **2** (15 mL, 12.86 g, 0.178 mol) and the resultant mixture was stirred at 80 °C for 16 h. After cooling, the reaction mixture was diluted with EtOAc (150 mL), washed with water and then dried ($MgSO_4$). Evaporation of the solvent in vacuo gave an oily residue which was shown by HPLC analysis to be a mixture of three compounds. This mixture was separated by column chromatography (hexane/acetone, 10 : 0.5) to afford compounds **5**, **9** and **12a**; yields: 2.97 g (11%), 9.71 g (31%) and 0.68 g (1.4%), respectively.

Compound **5**:

Mp 122 °C (Lit.[6] 122–123 °C). TLC (hexane/acetone, 5:2): $R_f = 0.47$. HPLC (hexane/CH_2Cl_2/*i*-PrOH, 50:50:0.5): $R_t = 4.6$ min.

MS: $m/z = 207$ ($M^+ + 1$, 21), 206 (M^+, 100), 191 ($M^+ - CH_3$, 52), 163 ($M^+ - C_3H_7$).

Compound **9**:

Yellow oil. TLC (hexane/acetone, 5:2): $R_f = 0.56$. HPLC (hexane/CH_2Cl_2/*i*-PrOH, 50:50:0.5): $R_t = 4.3$ min.

IR (film): $\nu = 3500$ (OH), 1460, 1420, 1370, 1330, 1300, 1270, 1230, 1150, 1090, 1050 cm^{-1}.

^1H NMR ($CDCl_3$): $\delta = 0.61$ (3H, d, $J = 7$ Hz, CH_3), 1.04 (3H, d, $J = 7$ Hz, CH_3), 1.06 (3H, d, $J = 7$ Hz, CH_3), 1.14 (3H, d, $J = 7$ Hz, CH_3), 2.02 (1H, m, CH), 2.06 (3H, s, CH_3), 2.12 (3H, s, CH_3), 2.14 (3H, s, CH_3), 2.16 (1H, m, CH), 4.44 (1H, d, $J = 5$ Hz, CH), 4.55 (1H, s, OH), 4.99 (1H, d, $J = 2$ Hz, CH).

^{13}C NMR ($CDCl_3$): $\delta = 11.26$ (C-5-CH_3), 12.02 (C-7-CH_3 and C-8-CH_3), 14.80 (C-4-C-2'), 16.76 (C-2-C-2'), 17.17 (C-2-C-1'-CH_3), 19.98 (C-4-C-1'-CH_3), 32.64 (C-2-C-1'), 32.91 (C-4-C-1'), 77.90 (C-4), 109.59 (C-2), 116.65 (C-7), 121.42 (C-8), 122.07 (C-5), 122.56 (C-4a), 146.49 (C-6), 147.92 (C-8a).

MS: $m/z = 278$ (M^+, 40), 235 ($M^+ - C_3H_7$, 5), 206 [$M^+ - (CH_3)_2CHCHO$, 100].

Compound **12a**: See Tables 1 and 2.

Reaction of 2-Methylprop-2-en-1-ol (2) with 2,3-Dimethylhydroquinone (1b):

To a stirred solution of hydroquinone **1b** (5.0 g, 36 mmol) and (1*S*)-(+)-camphorsulfonic acid (0.5 g) in dry toluene (25 mL) was added alcohol **2** (5 mL, 4.29 g, 59 mmol) and the resulting mixture was stirred at 70 °C for 30 h. After cooling, the reaction mixture was diluted with EtOAc (200 mL) and successively washed with water and brine, and then dried ($MgSO_4$). Evaporation of the solvent gave a mixture of two compounds which was separated by column chromatography (hexane/acetone, 10 : 1) to furnish **12b** and **11b**; yield: 1.8 g (32%), 0.9 g (15%).

Compound **12b**: See Tables 1 and 2.

Downloaded by: Rice University. Copyrighted material.

Compound **11b**: Mp 221 °C. TLC (hexane/acetone, 5:2): $R_f = 0.4$.

IR (KBr): ν = 3350 (OH), 1600, 1580, 1460, 1430, 1400, 1380, 1320, 1260, 1200, 1050 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 0.83 (6H, d, J = 6.5 Hz, $2CH_3$), 1.95 (6H, s, $2CH_3$), 2.02 (6H, s, $2CH_3$), 2.24 (1H, m, CH), 3.97 (1H, d, J = 11 Hz, CH), 6.54 (2H, s, H_{arom}), 7.97 (2H, br s, 2OH), 8.46 (2H, s, 2OH).

^{13}C NMR (DMSO-d_6): δ = 12.00 (C-4′-CH_3 and C-4″-CH_3), 12.99 (C-3′-CH_3 and C-3″-CH_3), 21.62 (C-3 and C-2-CH_3), 30.63 (C-2), 43.85 (C-1), 110.61 (C-6′ and C-6″), 120.67 (C-4′ and C-4″), 124.79 (C-3′ and C-3″), 129.41 (C-1′ and C-1″), 144.27 (C-5′ and C-5″), 148.66 (C-2′ and C-2″).

MS: m/z = 330 (M^+, 25), 287 ($M^+ - C_3H_7$, 100), 269 (25), 257 (10), 241 (12).

Xanthenes 12a–g; General Procedure:

To a stirred mixture of hydroquinone **1** (0.1 mol) and TsOH (3 g) in the appropriate solvent (300 mL) was added alcohol **2** (0.06 mol) and the resulting suspension was stirred for the specified period of time at the temperature shown in Table 1. After cooling, Et_3N (2 mL) and Kieselgel (10 g) were added, and the mixture was stirred for 10 min, filtered, and the filtrate was evaporated in vacuo. The residue was recrystallized from EtOH or acetone. The yields of **12a–g** and their spectral data are summarized in Tables 1 and 2.

Reaction of 2-Methylprop-2-en-1-ol (2) with Methoxyhydroquinone (1f):

To a stirred mixture of hydroquinone **1f** (14.0 g, 0.1 mol) and (1*S*)-(+)-camphorsulfonic acid (1.0 g) in dry toluene (150 mL) was added alcohol **2** (4.0 g, 56 mmol) and the resulting mixture was stirred at 70 °C for 3 h. After cooling, the resulting precipitate was collected by filtration to give **11f** as a white powder; yield 15.5 g (92.8%), mp 180–181 °C. TLC (hexane/acetone, 5:2): $R_f = 0.15$.

IR (KBr): ν = 3400 (OH), 1510, 1500, 1460, 1380, 1360, 1280, 1220, 1200, 1170, 1080 cm^{-1}.

^1H NMR ($CDCl_3$ + DMSO-d_6): δ = 0.82 (6H, d, J = 6 Hz, $2CH_3$), 2.24 (1H, m, CH), 3.7 (6H, s, $2OCH_3$), 3.95 (1H, d, J = 11 Hz, CH), 6.42 (2H, s, H_{arom}), 6.58 (2H, br s, 2OH), 6.75 (2H, s, H_{arom}), 8.4 (2H, br s, 2OH).

^{13}C NMR (DMSO-d_6): δ = 21.62 (C-3 and C-2-CH_3), 30.16 (C-2), 43.47 (C-1), 55.82 ($2OCH_3$), 101.57 (C-3′and C-3″), 115.37 (C-6′ and C-6″), 123.12 (C-1′ and C-1″), 139.15 (C-5′ and C-5″), 145.50 (C-4′ and C-4″), 146.94 (C-2′ and C-2″).

2-(1-Hydroxy-2-methylpropyl)-3,5,6-trimethyl[1,4]benzoquinone (14a):

To a stirred solution of compound **9** (8.5 g, 30.5 mmol) in MeOH (430 mL) was added dropwise a solution of iron(III) chloride (123 g, 0.76 mol) in MeOH (1300 mL) and water (270 mL) and the resultant mixture was stirred at r.t. for 2 h. The reaction mixture was diluted with water (600 mL) and extracted with EtOAc (2 × 400 mL). The combined EtOAc solutions were successively washed with water and brine, and then dried ($MgSO_4$). Evaporation of the solvent gave an oily residue which was purified by column chromatography (hexane/acetone, 10:0.5) to yield **14a** (4.6 g, 67.9%) as a light yellow oil. TLC (hexane/acetone, 5:2): $R_f = 0.7$.

HPLC (hexane/CH_2Cl_2/*i*-PrOH, 50:50:0.5): R_t = 13.9 min.

IR (film): ν = 3500 (OH), 1620 (quinone), 1460, 1420, 1360, 1270, 1245, 1220, 1120, 1090 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.80 (3H, d, J = 7 Hz, CH_3), 1.12 (3H, d, J = 6.5 Hz, CH_3), 2.01 (3H, s, CH_3), 2.03 (3H, s, CH_3), 2.06 (3H, s, CH_3), 2.15 (1H, m, CH), 3.64 (1H, d, J = 11 Hz, exchangeable with D_2O, OH), 4.28 (1H, dd, J = 9 and 11 Hz, CHO).

^{13}C NMR ($CDCl_3$): δ = 11.78 (C-3-CH_3), 11.90 (C-5-CH_3), 12.25 (C-6-CH_3), 19.12 (C-3′), 19.30 (C-2′–CH_3), 34.39 (C-2′), 76.22 (C-1′), 140.72 (C-5), 140.90 (C-6), 141.34 (C-3), 142.27 (C-2), 187.08 (C-4), 188.98 (C-1).

14a-Acetate (14b):

Prepared by standard method from **14a** (1.8 g, 8.1 mmol), pyridine (1.5 mL) and Ac_2O (2.5 g, 24.5 mmol) in CH_2Cl_2 (10 mL); yield 1.5 g (70%) of **14b**. TLC (hexane/acetone, 5:2): $R_f = 0.58$.

IR (film): ν = 1725 (CO), 1640 cm^{-1} (quinone).

^1H NMR ($CDCl_3$): δ = 0.80 (3H, d, J = 7 Hz, CH_3), 1.05 (3H, d, J = 6.5 Hz, CH_3), 2.00 (6H, s, $2CH_3$), 2.04 (3H, s, CH_3), 2.14 (3H, s, CH_3), 2.4 (1H, m, CH), 5.61 (1H, d, J = 9 Hz, CH).

14a-Benzoate (14c):

Prepared by standard procedure from **14a** (1.8 g, 8.1 mmol), pyridine (1.5 mL) and benzoyl chloride (1.35 g, 9.6 mmol) in CH_2Cl_2 (10 mL); yield 1.9 g (72%) of **14c**. TLC (hexane/acetone, 5:2): $R_f = 0.66$.

IR (film): ν = 1715 (CO), 1640 cm^{-1} (quinone).

^1H NMR ($CDCl_3$): δ = 0.90 (3H, d, J = 7 Hz, CH_3), 1.15 (3H, d, J = 6 Hz, $2CH_3$), 2.00 (6H, s, $2CH_3$), 2.20 (3H, s, CH_3), 2.50 (1H, m, CH), 5.85 (1H, d, J = 10 Hz, CH), 7.5 (3H, m, H_{arom}), 8.0 (2H, m, H_{arom}).

1,1-Bis(3,4,6-trimethyl-2,5-dioxocyclohexa-3,6-dien-1-yl)-2-methylpropane (13a):

To a stirred solution of compound **12a** (3.9 g, 11.6 mmol) in MeOH (100 mL) was added dropwise a solution of iron(III) chloride (39.6 g, 0.244 mol) in MeOH (200 mL) and water (40 mL) and the resulting mixture was stirred at r.t. for 2 h. The precipitated product was filtered off and recrystallized from MeOH to afford 3.5 g (86.3%) of **13a**, as yellow needles; mp 176 °C. TLC (hexane/acetone, 5:2): $R_f = 0.68$. HPLC (hexane/CH_2Cl_2/*i*-PrOH, 50:50:0.5): R_t = 13.5 min.

IR (KBr): ν = 1630 (quinone), 1600, 1460, 1420, 1365, 1270, 1240, 1210, 1120, 1100, 1050 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.91 (6H, d, J = 6 Hz, $2CH_3$), 1.98 (12H, s, $4CH_3$), 2.29 (6H, s, $2CH_3$), 2.99 (1H, m, CH), 4.09 (1H, d, J = 11 Hz, CH).

^{13}C NMR ($CDCl_3$): δ = 12.29 (C-6′-CH_3 and C-6″-CH_3), 12.55 (C-5′-CH_3 and C-5″-CH_3), 13.66 (C-3′-CH_3 and C-3″-CH_3), 22.11 (C-3 and C-2-CH_3), 28.87 (C-2), 48.59 (C-1), 140.03 (C-6′ and C-6″), 143.19 (C-3′ and C-3″), 143.95 (C-2′ and C-2″), 187.41 (C-1′ and C-1″), 187.73 (C-4′ and C-4″).

MS: m/z = 354 (M^+, 70), 339 ($M^+ - CH_3$, 26), 311 ($M^+ - C_3H_7$, 100), 297 (18), 283 (13), 269 (38), 253 (8), 241 (10).

1,1-Bis(3,4-dimethyl-2,5-dioxocyclohexa-3,6-dien-1-yl)-2-methylpropane (13b):

To a stirred solution of compound **12b** (3.0 g, 9.6 mmol) in MeOH (75 mL) was added dropwise a solution of iron(III) chloride (40.0 g, 0.25 mol) in MeOH (420 mL) and water (40 mL) and the resulting mixture was stirred at r.t. for 2 h. The reaction mixture was diluted with water (600 mL) and extracted with EtOAc (2 × 750 mL). The combined EtOAc solutions were successively washed with water and brine, and then dried ($MgSO_4$). Evaporation of the solvent gave an oily residue which was purified by column chromatography (hexane/acetone, 10:0.5) to afford **13b** (1.45 g, 46.3%) as a yellow semisolid oil. TLC (hexane/acetone, 5:2): $R_f = 0.62$.

IR (film): ν = 1620 (quinone), 1480, 1450, 1430, 1360, 1300, 1250, 1225, 1140, 1090 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.92 (6H, d, J = 6.5 Hz, $2CH_3$), 2.00 (12H, s, $4CH_3$), 2.18 (1H, m, CH), 4.00 (1H, d, J = 10 Hz, CH), 6.59 (2H, d, J = 1 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 11.96 (C-6′-CH_3 and C-6″-CH_3), 12.57 (C-5′-CH_3 and C-5″-CH_3), 21.24 (C-3 and C-2-CH_3), 30.30 (C-2), 44.08 (C-1), 133.50 (C-3′ and C-3″), 140.67 (C-5′ and C-5″), 141.40 (C-6′ and C-6″), 148.45 (C-2′ and C-2″), 186.36 (C-1′ and C-1″), 187.33 (C-4′ and C-4″).

MS: m/z = 326 (M^+, 100), 311 ($M^+ - CH_3$, 22), 283 ($M^+ - C_3H_7$, 62), 269 (12), 255 (13), 241 (20), 227 (14).

Preparation of Xanthene Derivatives 12aa–12fa: General Procedures:

2,7-Dialkoxyxanthene Derivatives:

To a stirred suspension of xanthene **12a–g** (23 mmol) and NaOH (4 g) in water (40 mL) was added dialkyl sulfate (0.1 mol) and the

Downloaded by: Rice University. Copyrighted material.

resulting mixture was stirred at r.t. overnight. The mixture was filtered, the solids were washed with water and crystallized from EtOH.

2,7-Diacyloxyxanthene Derivatives:

To a stirred solution of xanthene **12a–g** (10 mmol) in dry pyridine (15 mL) was added dropwise Ac_2O or benzoyl chloride (25 mmol) and the resultant mixture was stirred at r.t. overnight. The reaction mixture was poured into ice/water and acidified by dropwise addition of concentrated HCl. The resulting suspension was filtered, the solids were washed with water and then recrystallized from EtOH.

2,7-Di(2-dialkylaminoethyloxy)xanthene Derivatives:

To a stirred mixture of xanthene **12a–g** (5 mmol), NaOH (22 mmol) and KI (0.2 g) in dry dioxane (100 mL) was added portionwise 2-dialkylaminoethyl chloride hydrochloride and the resulting mixture was stirred at r.t. for 48 h. The reaction mixture was diluted with Et_2O (200 mL), washed with water, dried ($MgSO_4$) and then treated with gaseous HCl. The precipitated HCl salt was filtered and recrystallized from a mixture of CH_2Cl_2 and EtOH.

Financial support from EGIS Pharmaceutical Work (Budapest) and Hungarian OTKA Foundation are gratefully acknowledged.

(1) Tarbell, D.S. *Org. React.* **1944**, *2*, 2.
(2) Murray, A.W. *Org. React. Mech.* **1980**, 517.
(3) Lutz, R.P. *Chem. Rev.* **1984**, *84*, 205.
(4) Ziegler, F.E. *Chem. Rev.* **1988**, *88*, 1423.
(5) Novák, L.; Kovács, P.; Kolonits, P.; Szántay, Cs. *Heterocycles* **1994**, *38*, 177.
(6) Lars, J.; Nilsson, G.; Selander, H.; Sievertsson, H.; Skånberg, I. *Tetrahedron* **1970**, *26*, 879.
(7) Burton, G.W.; Doba, T.; Gabe, E.J.; Hughes, L.; Lee, F.L.; Prasad, L.; Ingold, K.U. *J. Am. Chem. Soc.* **1985**, *107*, 7053.
(8) Baker, W. *J. Chem. Soc.* **1941**, 662.
(9) Hardegger, E.; Steiner, K.; Widmer, E.; Conodi, H.; Schmidt, Th.; Knoepfel, H.P.; Rieder, W.; Meyer, H.J.; Kugler, F.; Gempeler, H. *Helv. Chim. Acta* **1964**, *47*, 1996.
(10) Shah, R.C.; Mehta, C.R.; Wheeler, T.S. *J. Chem. Soc.* **1938**, 1556.
(11) Mandell, L.; Roberts, E.C. *J. Heterocycl. Chem.* **1965**, *2*, 479.

Downloaded by: Rice University. Copyrighted material.